

**Remarks**

**Status of the Claims**

Following amendment as requested herein, the following claims are now pending in the present application: 1, 11-16, 19-27, 32-40, and 43. Of these, Claims 36-40 and 43 were withdrawn. By this Amendment, Claim 26 is amended to remove the carboxamide compound not within the scope of Claim 1, from which Claim 26 depends.

**Oath/Declaration**

The Office Action stated that a new Oath or Declaration was required, to correct a typographical error in the filing date of PCT/GB02/02563. A new Declaration is attached, correcting this typographical error.

**Rejections Under 35 U.S.C. § 112, Second Paragraph**

Claim 26 was rejected under 35 U.S.C. §112, second paragraph, as indefinite. The basis for the rejection was that Claim 26, which depends from Claim 1, included a compound not within the scope of Claim 1 as amended. Claim 26 has been amended to remove this compound. Accordingly, the rejection should be withdrawn.

**Rejections under 35 U.S.C. § 103(a)**

Claims 1, 11-16, 19-27 and 32-35 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over EP 0 512 675 to Allen et al. ("Allen"). This rejection is respectfully traversed.

EP 512 675 discloses compounds that contain an imidazole ring, which corresponds to the X<sub>1</sub> to X<sub>4</sub>-containing ring of the compound of Formula I. The Office Action acknowledges that the presently-claimed compounds are distinguished from Allen in view of the fact that the 2-position of the imidazole ring (as defined by "-ER<sup>1</sup>" in Claim 1 of EP 512 675 at pages 68 to 69) has to represent a substituent, whereas, when the X<sub>1</sub> to X<sub>4</sub>-containing

ring according to the present claims represents an imidazole ring, then the corresponding 2-substituent (as defined by  $R^1$ , when  $X_1$  represents  $-C(R^1)-$ ) can only represent hydrogen.

The purported basis for the rejection (i.e., at pages 7 and 8 of the Office Action) is that the modification (i.e. replacing the 2-substituent with a hydrogen atom to provide a 2-unsubstituted imidazole) would be an obvious modification of the prior art to arrive at the present invention. This is on the basis that *"those skilled in [the] chemical art [would appreciate that] one homologue is not such an advance over [an] adjacent member of [the] series as requires invention because chemists knowing properties of one member of [the] series would in general know what to expect in adjacent members. The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (i.e, an **angiotension II antagonist**)"* (emphasis added).

In this respect, Applicants respectfully point out a key difference between the disclosure of EP 512 675 and the present case. While the prior art document discloses angiotensin II (AngII) **antagonists**, the compounds of the present invention have found utility as being useful angiotensin II **agonists**.

The Examiner has provided no evidence to suggest why the skilled person would expect the pharmacological activity to completely change as a result of changing the prior art components to those presently claimed, nor indeed why that person would, when searching for compounds that act as Ang II agonists, start from a prior art document that related to Ang II antagonists.

The Office Action also appears to suggest that, because the prior art document states that the antagonists disclosed therein are useful for treating hypertension, it would be obvious that the presently-claimed compounds would also be useful in treating hypertension (which is one of the conditions presently claimed in this case).

Firstly, the Office Action has not provided any cogent argumentation in relation to why the claimed modification is obvious in a purely structural sense, taking the cited prior art document into consideration in isolation.

Secondly, the fact that the Applicant has surprisingly found that the presently-claimed, novel compounds are useful as Ang II agonists is a feature that is non-obvious *per se*, providing a completely different type of utility to those compounds disclosed in the cited prior art.

The Office Action states at page 7 of the action that *"It is well established that the substitution of a hydrogen atom for a lower alkyl on a known compound is not a patentable modification absent unexpected or unobvious results"*. Surely, when such a modification completely changes the nature of the pharmacological activity of the compounds, this has to be regarded as an unexpected and unobvious result. Indeed, this has to be put in the context of the fact that it is extremely rare in the pharmacological art to render compounds that are small molecules that have agonist activity at *any* receptor. Normally small molecules tend to have antagonist activity.

In this respect, the fact that similar diseases may be treated as a result of the newly found utility is, respectfully, largely irrelevant. There are many different ways of treating hypertension, just as there are many different ways of treating other diseases. When an inventor finds a new way of treating a known condition by way of making a structural modification that leads to a completely different class of activity in the treatment of the same condition, under U.S. patent law, this is a patentable invention.

Thus, the newly-discovered pharmacological effect provided by the present invention provides the public with a completely new invention, which could in no way have been derived from the cited prior art.

Thirdly, Applicants respectfully point out that, as stated in the application at page 6 to 9, the compounds presently claimed are not only agonists of AngII, but are, more specifically, agonists of the angiotensin II type 2 (the AT2) sub-receptor. In particular, they

are agonists that bind selectively to that sub-receptor. This is positively demonstrated by way of the data described in Example 14 (see page 64), where it is stated that the compounds of the examples were all found to exhibit an affinity for AT2 receptors of less than  $K_i = 100$  nM and an affinity for the other angiotensin II receptor (AT1) of more than  $K_i = 500$  nM. Thus, this activity could in no way have been predicted from what was known from the cited prior art or other prior documents which the applicants are aware.

Hence, not only is there no suggestion in the cited prior art document of the utility of the compounds disclosed therein as Ang II agonists, there is further no suggestion of their utility as, specifically, selective AT2 sub-receptor agonists.

**Rejoinder of Process for Preparation Claims/  
Presentation of Method of Treatment Claims**

As discussed with the Examiner in the telephonic interview held on April 5, 2007, Applicants would be permitted to rejoin process for preparation claims, and the Examiner would consider certain method of treatment claims, directed to the compounds the Examiner agreed were allowable (i.e., if Claim 1 was amended to incorporate the limitations of Claim 18). Now that the Examiner has rejected Claim 1, amended as previously agreed, and Applicants arguments are believed to overcome that rejection, Applicants respectfully request that such process for preparation and method of treatment claims be considered and found to be allowable.

Should the Examiner be inclined to allow the compound claims, but consider the method claim to be unpatentable for any reason, she is encouraged to contact the undersigned Applicants' representative to discuss changes that might be made to these claims so that the application is in condition for allowance.

### **Conclusion**

In view of the amendments and comments presented herein, Applicants respectfully submit that the application is in condition for allowance, and prompt notification of same is earnestly solicited.

The Examiner is encouraged to contact the undersigned with any questions she may have, and if the Examiner is not inclined to allow any or all of the claims, to also issue an Advisory Action providing reasons for such non-allowance.

The Director is hereby authorized to charge any fee that may be required, if any, to Womble Carlyle's Deposit Account No. 09-0528.

Respectfully submitted,

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